Non-technical Abstract

The average survival time for patients with unresectable or recurrent refractory squamous cell carcinoma of the head and neck is approximately 6 months, with 20% of patients surviving at 1 year. There is evidence that the poor prognosis of advanced head and neck cancer may be associated with alterations in the body's immune system, and treatment with agents that modulate the immune system may be effective in restoring an immune response against the tumor. Cytokines are believed to be important in modulating the body's response against cancer. They are an important component of the immune system which participate in the development of the immune response. Gene therapy with immunomodulators such as the interferons and interleukins may provide successful alternatives to, or adjuvants to radiotherapy/chemotherapy and/or surgery.

Human IL-12 mediates a number of biological activities and can enhance the proliferation and cytolytic function of T-cells and natural killer (NK) cells (23,24,25). IL-12 induces T-cells and NK cells to produce a number of other cytokines, including IFN-γ, tumor necrosis factor (TNF), IL-2, IL-3, IL-8, IL-10, and colony-stimulating factors. IL-12 also stimulates the generation of T-helper type 1 (Th1) effector cells during an immune response. IL-12 can also inhibit growth-factor-induced angiogenesis (26,27,28) thereby slowing tumor growth. IFN-γ is believed to have many biological effects which could influence tumor growth (28). Other studies have also suggested a role for endogenous IL-12 in disease pathophysiology (29,30). Lissoni et. al. (31) evaluated serum levels of endogenous IL-12 in a group of patients with non metastatic and metastatic solid tumor in relation to the survival time as compared to a group of patients treated with IL-2.

In animal models, the partial or complete regression of several types of tumors has been observed following direct intratumoral administration of IL-12 Gene Medicine, a non-viral gene therapy consisting of a plasmid which expresses human interleukin-12 formulated with the synthetic polymer polyvinylpyrrolidone in 0.9% Sodium Chloride for Injection, U.S.P. When administered intratumorally to tumor-bearing mice, IL-12 Gene Medicine leads to a decrease in the rate of tumor progression, with complete tumor regression in some cases. In cases where tumor rejection occurs, the animals also demonstrate immunity to re-challenge with the same tumor cell type. These data suggest that administration of the IL-12 Gene Medicine leads to the generation of an anti-tumor immune response. It is anticipated that the anti-tumor immune response will promote tumor regression, inhibition of tumor progression, and/or prevention of metastasis in humans.

The clinical studies proposed are directed at expressing human IL-12 at a tumor site by non-viral, polymer-mediated delivery of a gene encoding IL-12 This gene transfer is intended to induce expression of IL-12 in or around the tumor at levels sufficient to promote an anti-tumor response without high concentrations of IL-12 protein in the bloodstream. In animal experiments conducted to address this particular safety issue, a concentration of IL-12 plasmid DNA sufficient to bring about an anti-tumor response did not lead to levels as high as reported in the literature for the recombinant protein on a mg/kg basis. In addition, preclinical toxicology testing in nonhuman primates demonstrated the absence of side effects of IFN-α Gene Medicine through the highest dose tested, 12 mg/kg. This approach offers a distinct advantage over the systemic administration of the recombinant protein.